Sugar-responsive block copolymers by direct RAFT polymerization of unprotected boronic acid monomers†

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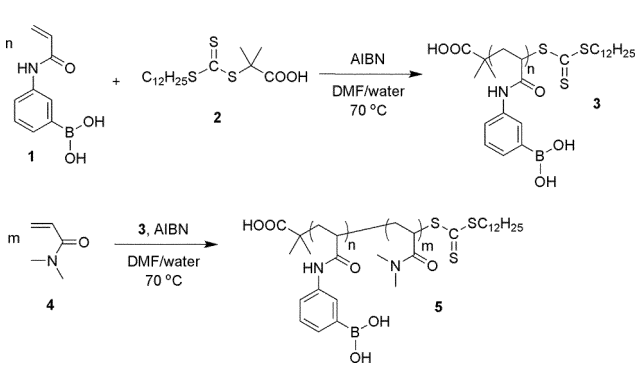
Novel sugar-responsive block copolymers were prepared by RAFT block copolymerization of unprotected boronic acid monomers, providing a direct route to supramolecular assemblies that dissociate upon the addition of glucose.

Boronic acid-containing polymers demonstrate unique reactivity and self-assembly capability that allow potential applications as self-healing materials, flame retardants, separating agents, therapeutic agents, self-regulated drug delivery systems, and sensors for sugars and glycoproteins.[1,2] To date, the synthesis of free boronic acid-containing polymers by conventional radical polymerization has resulted in ill-defined random copolymers or crosslinked gels.[3–5] While the robust nature of radical polymerization provides a facile route by which to polymerize many functional vinyl monomers, the inability to prepare well-defined (co)polymers with controlled topology significantly limits utility in many advanced applications. In particular, to more fully capitalize on the potential of boronic acid-containing macromolecules in sensing and delivery applications that rely on supramolecular self-assembly (*e.g.*, block copolymer micellization), it is essential to prepare boronic acid (co)polymers in a facile manner with precise control over molecular weight, chain architecture, and composition.[6]

Controlled/"living" radical polymerization (CRP) provides accessibility to polymers with predictable molecular weights, narrow molecular weight distributions, and preserved chain end functionalities, the latter of which allows block copolymer formation.[7] Of the various methods of CRP, atom transfer radical polymerization (ATRP)[8] and reversible addition–fragmentation chain transfer (RAFT) polymerization[9,10] have been employed to prepare well-defined organoboron polymers. For example, Jäkle *et al.* reported the synthesis of boron-containing (co)polymers *via* ATRP of organoboron monomers or silylated precursors that were borylated through post-polymerization modification.[11] Borylation and subsequent hydrolysis of a block copolymer with trimethylsilyl-functionalized polystyrene units led to boronic acid block copolymers capable of micellization in THF–water mixtures. We recently employed RAFT for the polymerization of a styrenic boronic ester, and subsequent post-polymerization deprotection led to well-defined boronic acid homo- and block copolymers.[6]

As opposed to these previously reported methods, an attractive alternative approach to well-defined boronic acid (co)polymers is the direct controlled polymerization of free, unprotected boronic acid monomers.[12] In order to realize this goal, a mechanism suitable for controlling the polymerization of functional, Lewis acidic monomers is required. Herein, we report the RAFT homo- and block (co)polymerization of a free boronic acid acrylamido monomer. This represents the first example of well-defined boronic acid-containing block copolymers being prepared directly by any method, and as such, represents an advancement in the synthesis of functional, organometallic polymeric materials. We also describe the solution properties of amphiphilic block copolymers that result from copolymerization of a free boronic acid monomer with a hydrophilic monomer. While the field of stimuli-responsive block copolymers includes vast examples of, *e.g.*, temperature-responsive systems, the block copolymers described herein self-assemble–dissociate in response to changes in pH *and*, importantly, the concentration of diols in the surrounding medium. The latter aspect provides a route to saccharide-responsive block copolymers.

The particular choice of RAFT polymerization was based on its functional group tolerance and particular applicability for the synthesis of well-defined, water-soluble acrylamido polymers.[9,13] 3-Acrylamidophenylboronic acid[14] (APBA, **1**) was polymerized with 2-dodecylsulfanylthiocarbonylsulfanyl-2-methylpropionic acid[15] (DMP, **2**) as the chain transfer agent (CTA) and 2,2′-azobisisobutyronitrile (AIBN) as the initiator at 70 °C in 95% DMF–5% water (Scheme 1). The molar ratio



Scheme 1 Synthesis of 3-acrylamidophenylboronic acid homo- and block copolymer by reversible addition–fragmentation chain transfer (RAFT) polymerization.

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of [monomer] : [CTA] : [initiator] was varied to observe the effect on polymerization kinetics and molecular weight control. After a brief inhibition period, pseudo first-order kinetics were observed up to high conversion (Fig. 1A). Molecular weight analysis by size exclusion chromatography (SEC) necessitated protection of the boronic acid residues by esterification with pinacol, after which good agreement between theoretical and experimental molecular weights was observed. For instance, with [monomer] : [CTA] : [initiator] = [100] : [1] : [0.2], 67% conversion was obtained in 150 min, resulting in polymer with M_n = 19 200 g mol^{-1} (M_w/M_n = 1.13), in good agreement with the theoretical M_n of 18 500 g mol^{-1}. During polymerization, the M_n of poly(3-acrylamidophenylboronic acid) (PAPBA, **3**) increased linearly with a slight deviation at low conversion, potentially due to inefficient chain transfer early in the polymerization (Fig. 1B). Despite this, the molecular weight distributions for the polymers remained narrow (M_w/M_n = 1.04–1.16) throughout the polymerizations (Table 1).

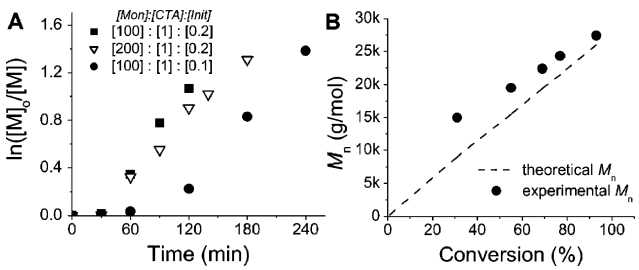


Fig. 1 (A) Pseudo first-order kinetic plot with selected molar ratios of monomer (M) : chain transfer agent (CTA) : initiator (I); (B) M_n *versus* monomer conversion ([Mon] : [CTA] : [Init] = 100 : 1 : 0.1) for RAFT homopolymerizations of 3-acrylamidophenylboronic acid (APBA, **1**) at 70 °C in 95% DMF–5% water.

PAPBA homopolymers were used as macro-chain transfer agents (macroCTAs) to synthesize diblock copolymers with *N*,*N*-dimethylacrylamide (DMA, **4**). ^{1}H NMR and SEC analyses of the resulting block copolymer confirmed successful incorporation of DMA. After copolymerization of DMA with a PAPBA macroCTA (**3**) of M_n = 25 000 g mol^{-1}, the molecular weight of the resulting block copolymer increased to M_n = 38 700 g mol^{-1} ($M_{n,theory}$ = 35 000 g mol^{-1}), and a new signal in the ^{1}H NMR spectrum was observed at δ = 2.93 ppm, arising from the methyl groups of the poly(*N*,*N*-dimethylacrylamide) (PDMA) units. Block copolymer formation was confirmed by comparison of the SEC molecular weight distributions (ESI†), though low molecular weight tailing may indicate either the presence of a small amount of dead macroCTA or inefficient pinacol protection prior to analysis. Nonetheless, the polydispersity index (M_w/M_n) of the resulting block copolymer remained below 1.2. Block copolymer compositions calculated with data from both ^{1}H NMR spectroscopy and SEC were in good agreement.

The solution behavior of the resulting block copolymers is of particular interest. Boronic acids are uniquely stimuli-responsive, in that their water solubility is tunable by changes in both pH and solution diol concentration, the latter of which has led to boronic acids being exploited as saccharide receptors.[2] In aqueous media, boronic acids exist in equilibrium between forms that are neutral (typically insoluble) (**6**) and anionic (soluble) (**7**) (Scheme 2).[16] Cyclic ester complexes between **6** and 1,2- or 1,3-diols are usually hydrolytically unstable, but **7** readily forms boronate esters (**8**) in the presence of vicinal diols.[17] An increase in concentration of **8** shifts the ionization equilibria, effectively lowering the pK_a of the acid. Thus, complexation adjusts the overall equilibrium from neutral/insoluble boronic acid moieties to anionic/hydrophilic boronates. Therefore, the extent of ionization (and water solubility) of boronic acid-containing polymers increases with diol concentration.[4,18] This principle was exploited to induce self-assembly of the PAPBA-*b*-PDMA block copolymers at pH < pK_a of the boronic acid, and the subsequent diol (glucose)-dependent solubility was used to trigger aggregate dissociation.

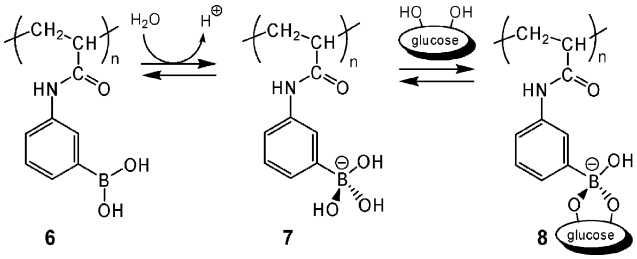
Dynamic light scattering (DLS) was employed to investigate the preliminary solution behavior of the double-hydrophilic block copolymers. PAPBA-*b*-PDMA was expected to be both pH- and diol-sensitive. pH sensitivity arises as a result of the responsive organoboron block remaining soluble above the pK_a of its boronic acid moieties. PAPBA$_{131}$-*b*-PDMA$_{138}$ was dissolved at pH 10.7 to give unimers with a hydrodynamic diameter (D_h) of approximately 7 nm (Fig. 2). When the pH was slowly reduced below the pK_a of the PAPBA block (p$K_a \approx 9$)[5] by dialysis against deionized water, it was expected that self-assembly would lead to micelles. Indeed, aggregates with an average hydrodynamic diameter of 35 nm were observed by DLS (Fig. 2). While we cannot be certain of the exact solution morphology, it is reasonable to assume the aggregates are micelles composed of a hydrophilic PDMA corona and a hydrophobic PAPBA core.

In addition to pH susceptibility, PAPBA-*b*-PDMA was also expected to respond to the concentration of diols in the

Table 1 Reversible addition–fragmentation chain transfer (RAFT) homo- and block copolymerization of 3-acrylamidophenylboronic acid (APBA, **1**) at 70 °C

	[M] : [CTA] : [I][a]	Conv.[b] (%)	$M_{n,theo}$[b]/g mol^{-1}	M_n[c]/g mol^{-1}	M_w/M_n[c]
PAPBA	[100] : [1] : [0.1]	71	19 500	19 700	1.16
PAPBA	[100] : [1] : [0.2]	67	18 500	19 200	1.13
PAPBA	[200] : [1] : [0.1]	74	40 600	37 800	1.16
PAPBA-*b*-PDMA[d]	[100] : [1] : [0.2]	96	35 000	38 700	1.17

[a] Molar ratio of monomer (M) : chain transfer agent (CTA) : initiator (I). [b] Determined by ^{1}H NMR spectroscopy (theoretical molecular weights ($M_{n,theo}$) calculated assuming 100% protection with pinacol). [c] Determined by SEC of the pinacol-protected polymers. [d] PAPBA-*b*-PDMA: PAPBA-*b*-poly(*N*,*N*-dimethylacrylamide).



Scheme 2 Ionization and diol complexation equilibria of boronic acids in aqueous media.

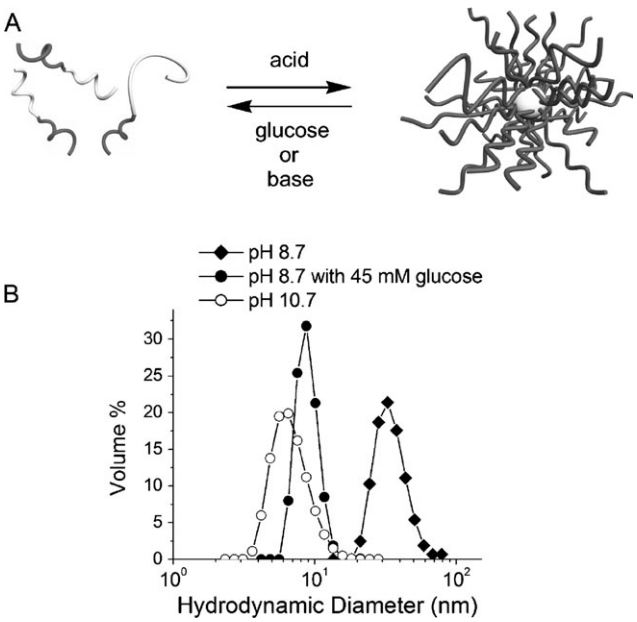


Fig. 2 (A) Block copolymer self-assembly–dissociation in response to changes in pH or [glucose]. (B) Aqueous hydrodynamic size distributions of poly(3-acrylamidophenylboronic acid)-*b*-poly(*N*,*N*-dimethylacrylamide) ($PAPBA_{131}$-*b*-$PDMA_{138}$) as a function of pH and [glucose] at 25 °C.

surrounding medium. Upon the addition of glucose to yield a final solution concentration of [glucose] = 45 mM (pH = 8.7), the average hydrodynamic diameter dramatically decreased to 9 nm, indicative of aggregate disassembly. Under these conditions, cyclic boronate ester formation between glucose and the boronic acid moieties of the PAPBA block led to both blocks of PAPBA-*b*-PDMA being soluble (Fig. 2).

The ability to prepare well-defined boronic acid-containing (co)polymers without resorting to protection–deprotection strategies may enable utilization of controlled topology organoboron polymers in a variety of biological and catalytic applications. For the first time, we have demonstrated a facile method to prepare block copolymers *via* direct RAFT polymerization of unprotected boronic acid monomers. In addition to expanding the range of functionality that can be directly incorporated into well-defined polymers, this route provides simplified access to a new class of "smart" block copolymers that demonstrate unique pH-, and more importantly, sugar-responsive self-assembly. In principle, the sensitivity of these copolymers is not limited to glucose. Our future investigations will explore other saccharides and/or naturally-occurring diols that also trigger aggregate disassembly.

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